REMARKS

Claims 1 and 3-21 were pending in the application. Claims 3 and 10-16 have been previously withdrawn by the Examiner, as being drawn to non-elected inventions or species. Claims 1, 4-9, and 17-21 were under consideration in the Office Action mailed December 4, 2007. Claim 19 has been canceled without prejudice. Support for the amendments to claim 1 may be found, at least, on page 5, lines 22-23 of and page 32, lines 13-14 of the specification. Support for the amendments to claims 5, 8, and 9 may be found, at least, on page 21, lines 1-5 of the specification. Support for the amendments to claim 20 may be found, at least, on page 5, lines 14-21 of the specification. Claims 4, 17, and 18 have been amended to correct typographical errors. Support for new claim 22 may be found, at least, on page 5, lines 19-20 of the specification. As of the instant response, claims 1, 3-18, and 20-22 are pending in the application and claims 1, 4-9, 17-18, and 20-22 are under consideration. No new matter has been added.

Amendment and/or cancellation of the claims should in no way be construed as acquiescence to any of the Examiner's rejections. The amendment and/or cancellation of the claims are being made solely to expedite prosecution of the present application and do not, and are not intended to, narrow the claims in any way. Applicants reserve the right to further prosecute the same or similar claims in the instant application, or in a divisional or continuation patent application.

Rejection of Claims 1, 4-9, and 17-21 Under 35 U.S.C. § 112, First Paragraph: Enablement

The Examiner has rejected claims 1, 4-9, and 17-21 under 35 U.S.C. § 112, as allegedly failing to comply with the enablement requirement, for the reasons of record, as specified below.

A. The Examiner contends that the specification does not provide a sufficient enabling description for a method of inhibiting the proliferation of lymphocytes by contacting them with a "soluble" form of B7-H3, as recited in claim 1. In the instant Office Action, the Examiner alleges that the amendment of claim 1 to recite an "activated" lymphocyte (in the response filed September 24, 2007, does not obviate the rejection of record. In the rejection of record, (Office Action mailed June 22, 2007), the Examiner states that:

> The instant specification discloses in Examples 4 and 5 that B7-H3 can inhibit activation of lymphocytes when present together with HLA-DR2 on the surface of a cell, or together with anti-CD3 antibody on the surface of a microbead (in cis configuration). At the same time, B7-H3 does not inhibit activation of lymphocytes when present on the surface of microbeads alone, even in the presence of other microbeads carrying anti-CD3 on their surface (trans configuration) (Example 5). Based on this disclosure, one of skill in the art would reasonably conclude that "soluble" B7-H3, i.e. not bound to a surface, and therefore not presented in proximity to either HLA-DR2 or anti-CD3 antibody, would not be able to inhibit activation of lymphocytes.

Applicants respectfully traverse the rejection. Although the specification teaches that B7-H3 transduces an inhibitory signal when expressed on the surface of a cell or coupled to a solid support (*i.e.,* microbead), the specification does not show or imply that soluble B7-H3 is incapable of transducing an agonistic signal. While the specification teaches that the experiments using CD3- and B7-H3-modified beads in the CIS and TRANS configurations "suggest that the B7-H3 receptor and the TCR need to be in close proximity for the downregulation of T cell activation" (page 56, lines 9-11 of the specification), the specification does not teach that B7-H3 must be surface-bound in order to transduce an agonistic signal. Moreover, one of ordinary skill in the art would expect that a soluble form of a B7-H3 protein would bind to its receptor, expressed on a T cell, in regions that include those in close proximity to the TCR (T cell receptor). Thus, there is no contradiction between the data presented in Examples 4 and 5, and the recitation of a "soluble" form of B7-H3 in claim 1. Applicants, therefore, respectfully request reconsideration and withdrawal of the rejection.

B. The Examiner contends that the specification does not provide sufficient enabling description for a method of inhibiting lymphocyte proliferation in a mammal afflicted with or at risk for an "immunologic disorder", as recited in claim 20. More specifically, the Examiner states that:

> [o]ne of skill in the art is aware that immunologic disorders include those which may benefit from inhibition of proliferation of lymphocytes, as well as those which will likely be aggravated by such inhibition (e.g. cancer, or conditions accompanied by insufficient immune responses).

Applicants respectfully traverse the rejection. However, solely in the interest of expediting prosecution of the instant application, Applicants have amended claim 20 to recite particular immunologic disorders. Applicants, therefore, respectfully request reconsideration and withdrawal of the rejection.

C. The Examiner contends that the specification does not provide a sufficient enabling description of how to make and use a polypeptide comprising an amino acid sequence which is "at least 90% identical" to the recited sequence, wherein the polypeptide competitively inhibits binding of B7-H3 to its receptor, as recited in claims 5, 8, and 9. More specifically, the Examiner states:

> In view of the unpredictability of the art, as addressed in the previous office action, the skilled artisan would not reasonably expect a generically recited polypeptide "at least 90% identical" to B7-H3 to share the same function as B7-H3, and thus there is insufficient guidance to direct the skilled artisan to such functional sequences.

Applicants respectfully traverse the rejection. In the previous Office Action (June 22, 2007), the Examiner cites Metzler *et al.*, (*Nature Structural Biology*, 1997, 4: 527-531; page 7, paragraph 4 of the Office Action) to provide support for the contention that single amino acid changes can result in alterations in the function of proteins. Metzler *et al.* discloses that certain mutations can alter or abolish the ability of CTLA4 to interact with its ligands CD80 and CD86. Applicants respectfully point out that the claimed methods, as currently amended, specify that the recited amino acid sequences satisfy a particular functional requirement, namely "wherein the soluble form exhibits a biological activity selected from the group consisting of decreasing T cell proliferation, decreasing secretion of IL-10, decreasing secretion of IFN-γ, decreasing secretion of GMCSF, and decreasing secretion of TNF-α." Applicants have amply enabled methods to determine whether or not a soluble B7-H3 protein would meet one of these requirements (see Examples 4 and 5 of the specification), and performing these methods would require only routine experimentation.

Moreover, Applicants teach the nucleic acid and amino acid sequences for human B7-H3 VC, human B7-H3 VCVC, and murine B7-H3. Applicants teach the signal, variable, constant, transmembrane, and cytoplasmic domains of these proteins (see, for example, Figure 1). Applicants teach conserved amino acids between the V1 and V2 regions of the human B7-H3 VCVC protein (see, for example, SEQ ID NO:8). Applicants teach fusions of human B7-H3 VC, human B7-H3 VCVC, and murine B7-H3 with heterologous peptides (see, for example, SEQ ID NOs:9-14). Applicants further teach conserved amino acids in the Ig V-like domain(s) of mammalian B7-H3 (see, for example, SEQ ID NO:15). Still further, Applicants teach individual highly conserved regions in the Ig V-like domain(s) of mammalian B7-H3 (SEQ ID NOs:16-22). Given the detailed structural and functional information taught in the specification,

as well as the teaching of specific assays for identifying B7-H3 activity, one of ordinary skill in the art would readily recognize that Applicants have enabled the claimed invention. Reconsideration and withdrawal of the rejection is, therefore, respectfully requested.

Rejection of Claims 1, 4-9, and 17-20 Under 35 U.S.C. § 102(a) and 102(e)

As the Examiner is aware, "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

While analyzing the Sequence Listing data, in response to the instant rejections under 35 U.S.C. § 102(a) and 102(e), Applicants became aware that the electronic version of the sequence listing contains an omission. Specifically, SEQ ID NO:8 was correctly listed in the paper version of the Sequence Listing submitted with the application, but inadvertently omitted from the electronic version. This results in the "n" sequence identifier referred to in the application corresponding with the "n-1" sequence identifier in the electronic version of the Sequence Listing, beginning with SEQ ID NO:9 in the application. For example, SEQ ID NO:9, as referred to previously in the application, actually corresponds to SEQ ID NO:8 in the electronic version of the Sequence Listing. Applicants regret the error and have submitted an updated electronic version of the Sequence Listing herewith.

With respect to the effect on the pending rejections under 35 U.S.C. § 102(a) and 102(e), Applicants note that, in the previous Office Action (mailed June 22, 2007), the Examiner alleged that SEQ ID NO:22, recited in claim 8, shared identity with amino acids 246-357 of SEQ ID NO:7 from Mikesell *et al.* The correct amino sequence for SEQ ID NO:22 was listed in the printed version of the Sequence Listing and its sequence identifier has been corrected (from SEQ ID NO:21 to SEQ ID NO:22) in the corrected electronic version, submitted herewith.

Also in the previous Office Action, the Examiner contended that SEQ ID NO:14, recited in claim 9, shared identity with amino acids 28-139 of SEQ ID NO:13 from Mikesell *et al.* The correct amino acid sequence for SEQ ID NO:14 was listed in the printed version of the Sequence

Listing and its sequence identifier has been corrected (from SEQ ID NO: 13 to SEQ ID NO:14) in the corrected electronic version, submitted herewith.

In the instant Office Action, the Examiner contends that the methods taught by Mikesell *et al.* "are not manipulatively different from the those instantly claimed, i.e. administering to a subject polypeptides which are within the scope of the instant claims, or contacting lymphocytes in vitro with the same polypeptides. Therefore, the outcome of performing the method steps taught by Mikesell et al. is inherently the same as that of the instantly claimed methods." The Examiner apparently relies on claim 28 of Mikesell *et al.* for support, as cited in the Office Action mailed June 22, 2007, since no additional citation for this argument has been provided in the instant Office Action.

Applicants respectfully traverse the rejection. Claim 28 of Mikesell *et al.* is drawn to a "method of **increasing or decreasing** T-cell activity in a subject" (emphasis added), comprising administering a pharmaceutical composition as recited in any one of claims 21-25. Claims 21-25 recite pharmaceutical compositions comprising nucleic acids, host cells, polypeptides, and antibodies. Mikesell *et al.* therefore claims that some of the pharmaceutical compositions increase T cell activity, while others decrease T cell activity. Analysis of the specification shows that Mikesell *et al.* states that BSL2 and BSL3 "acted as co-stimulatory molecules" (*i.e.,* increase T cell activity), while anti-BSL2 and anti-BSL3 antibodies "blocked the co-stimulatory effect" of BSL2 and BSL3 (*i.e.,* decrease T cell activity; see paragraph 330). Therefore, a method of "decreasing T-cell activity in a subject", as recited in claim 28 of Mikesell *et al.*, would clearly involve the administration of a pharmaceutical composition containing anti-BSL2 or anti-BSL3 antibodies (*i.e.,* claim 25), not the B7-H3 polypeptides of the instant claims.

Claim 1 has now been amended to indicate that the method be carried out "in a patient that may benefit from inhibition of lymphocyte activation". Mikesell *et al.* clearly do not contemplate administering a soluble form of B7-H3 to such a patient. In fact, the specification and claimed method of Mikesell *et al.* call for the administration of anti-BSL2 or anti-BSL3 antibodies under such circumstances. The claimed method is, therefore, novel and non-obvious over Mikesell *et al.* Applicants respectfully request reconsideration and withdrawal of the rejection.

Rejection of Claims 4-9 Under 35 U.S.C. § 112: Indefiniteness

The Examiner has rejected claims 4-9 under 35 U.S.C. § 112, for being indefinite, due to their dependence upon cancelled claim 2. Applicants have corrected the typographical error in claim 4, to make it dependent upon claim 1. Applicants, therefore, respectfully request reconsideration and withdrawal of the rejection.

Rejection of Claims 1 and 19-21 Under 35 U.S.C. § 112: Enablement

The Examiner has rejected claims 1 and 19-21 under 35 U.S.C § 112, as allegedly failing to comply with the enablement requirement. Specifically, the Examiner contends that "the specification does not provide a sufficient enabling description of a method of inhibiting lymphocyte proliferation 'in a mammal'" or a mammal afflicted with or at risk for an immunologic disorder. The Examiner then cites Blazar *et al.* (J. Immunol., 1996, 157: 3250-3259) as allegedly providing support for the assertion that factors such as tissue distribution, half-life, affinity, and avidity may be important in achieving a therapeutic effect. Moreover, the Examiner objects to the use of the term "at risk for" (claim 20), alleging that the burden of enabling prevention of a disease would be greater than enabling treatment.

Applicants respectfully traverse the rejection. As the Examiner is aware, "[a]n *in vitro*…model example in the specification, in effect, constitutes a 'working example' if that example 'correlates' with a disclosed or claimed method invention" (M.P.E.P. 2164.02). Moreover, if "a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonable correlating to the condition. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications)" (M.P.E.P. 2164.02).

Applicants submit that the CHO.HLA-DR2 cell / T cell activation model utilized in the instant application is a well-recognized model of human T cell activation. For example, Anderson *et al.* (Nature Biotechnology, 2000, 6: 211-214; cited in the Supplemental Information

Disclosure Statement submitted herewith) utilized this model as part of a study that provided a "theoretical framework for clinical trials in which co-stimulatory signals are manipulated in an attempt to modulate the immune response in human disease" (see Abstract and page 213, column 1). Applicants have demonstrated that B7-H3 modulates both proliferation of lymphocytes and production of multiple cytokines in this model (Example 4, page 53 of the specification). Applicants have also presented a detailed clinical protocol for the evaluation of therapeutic efficacy in psoriasis patients (Example 6, page 57 of the specification). Given the exemplification set forth in the specification, in a known and recognized model, a person of ordinary skill in the art could readily evaluate the inhibition of lymphocyte activation *in vivo*, and practice the claimed invention without undue experimentation. Applicants, therefore, respectfully request reconsideration and withdrawal of the rejection.

Moreover, solely in order to facilitate prosecution of the application, and in no way conceding the validity of the Examiner's rejection, Applicants have amended claim 20 to remove "at risk for". New claim 22 is directed to a method of treating a patient at risk for transplant rejection or graft-versus-host disease. One of ordinary skill in the art would readily recognize a patient "at risk" for one of these two immunologic disorders, namely, for example, those patients that are recipients of organ or bone marrow transplants. Applicants, therefore, respectfully request reconsideration and withdrawal of the rejection.

Rejection of Claims 1 and 4-9 Under 35 U.S.C. § 112, First Paragraph: Written Description

The Examiner has rejected claims 1 and 4-9 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Specifically, the Examiner alleges that Applicants were not in possession of the claimed method because Applicants were not in possession of a "B7-H3 receptor."

Applicants respectfully traverse the rejection and respectfully point out that only claims 5, 8, and 9 contain the language "B7-H3 receptor". Solely in order to facilitate prosecution of the application, and in no way conceding the validity of the Examiner's rejection, Applicants have amended claims 5, 8, and 9 to recite "a biological activity selected from the group consisting of decreasing T cell proliferation, decreasing secretion of IL-10, decreasing secretion of IFN-γ, decreasing secretion of GMCSF, and decreasing secretion of TNF-α", instead of

"competitively inhibits binding of B7-H3 to its receptor". Applicants, therefore, respectfully request reconsideration and withdrawal of the rejection.

CONCLUSION

If a telephone conversation with Applicants' Attorney would expedite the prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617)832-1000.

The Director is hereby authorized to charge any deficiency that should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our **Deposit Account No. 06-1448**, under Ref. No. **WYS-005.01**.

Respectfully submitted,

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